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One-pot, three-component synthesis of novel δ-sultam scaffolds via N-sulfonylation—intramolecular Michael sequences

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ABSTRACT

The synthesis of novel δ-sultam scaffolds utilizing one-pot, three-component reactions of 1,3-dicarbonyl compounds, primary aliphatic amines and substituted styrenesulfonyl chlorides is reported. A variety of six-membered sultams are obtained in moderate to good yields presumably via N-sulfonylation—intramolecular Michael addition sequences.

Sulfonamides have a rich chemical and biological history and are an important class of compounds in drug discovery due to their extensive chemical and biological activities.[1] Significant interest has been directed toward cyclic sulfonamides, also known as sultams. Although not found in nature, these compounds demonstrate a wide spectrum of activity.[2] Examples include the antiepileptic agent sulthiame,[3] the COX-2 inhibitor ampiroxicam,[4] and benzodithiazine dioxides displaying anti-HIV-1 activity[5] (Fig. 1). As chemically important materials, sultams have been utilized as efficient chiral auxiliaries and reagents.[6]

Sultams have traditionally been synthesized via cyclization protocols such as the Pictet–Spengler,[2a] and methods including Friedel–Crafts,[7] dianion alkylation,[8] cyclization of aminosulfonyl chlorides,[9] [3+2] cycloadditions,[10] and Diels–Alder reactions.[11] Recently, a number of transition metal catalyzed approaches to sultams have been reported, including the use of Pd,[12] Au,[13] Cu,[14] and Rh.[15]

Herein, we report the one-pot, three-component synthesis of novel δ-sultams via reaction of commercially available primary aliphatic amines and 1,3-dicarbonyl compounds with readily prepared substituted styrenesulfonyl chlorides.[16]

In a model experiment enaminone **3a**, obtained from the reaction of primary amine **1a** with β-ketoester **2a**, was treated with styrenesulfonyl chloride (**4a**) in CH_2Cl_2 at room temperature. The reaction proceeded smoothly and was complete within 12 h, affording the sultam **5a** in 76% yield (Scheme 1a).

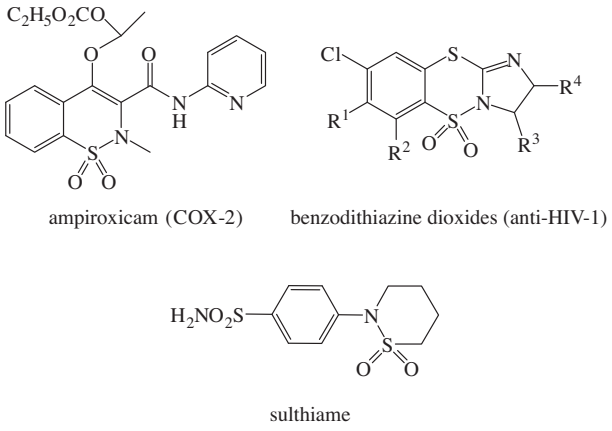

Figure 1. Biologically active six-membered sultams.

Further studies revealed that **5a** could be prepared via a one-pot reaction. This involved successive addition of amine **1a** and styrenesulfonyl chloride (**4a**) to a solution of β-ketoester **2a** in CH_2Cl_2 at room temperature (Scheme 1b).[17] Therefore, enaminone **3a** may be implicated in this three-component reaction. The structure of **5a** was confirmed on the basis of analytical data.[18]

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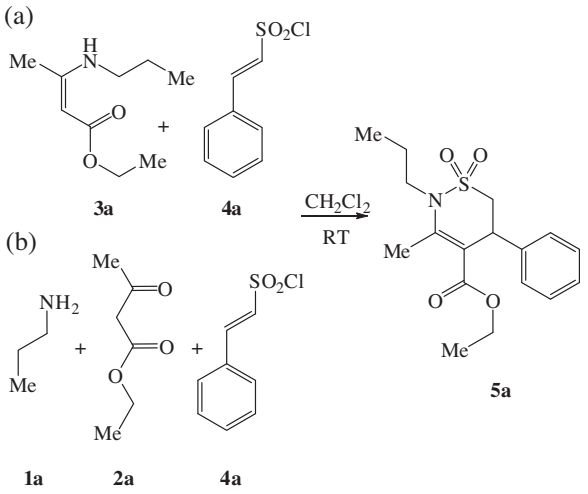


Scheme 1. Synthesis of sultam **5a** from: (a) the two-component reaction of **3a** and **4a**, and (b) the three-component reaction of **1a**, **2a,** and **4a**.

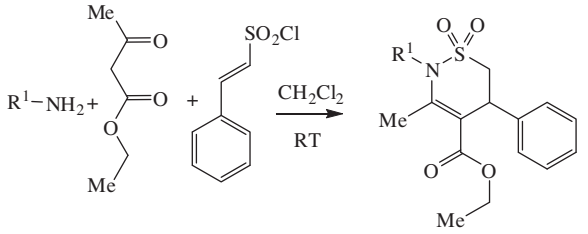
We next examined several primary amines **1a–e**, in the coupling of β-ketoester **2a** with styrenesulfonyl chloride (**4a**) using our one-pot method (Table 1). Whereas linear amines afforded the sultams in good yields (entries 1, 2 and 5, Table 1), lower yields were obtained with branched amines (entries 3 and 4, Table 1). Compared to linear amines, *sec*-butylamine, and cyclohexylamine with increased steric crowding about the nitrogen atom would be expected to react more slowly with styrenesulfonyl chloride (**4a**).

To further explore the scope of this reaction, several 1,3-dicarbonyl compounds **2a–c** and substituted styrenesulfonyl chlorides **4a–c** were examined (Scheme 2, Table 2). The analytical data including IR, ^{1}H NMR, and ^{13}C NMR spectra of the products **5f–o** were in agreement with the proposed structures.[19] Confirmation of the product structure was obtained by single crystal X-ray diffraction of δ-sultam **5m** (Fig. 2).[20]

The results shown in Table 2 reveal that dicarbonyl compounds either in the form of β-ketoesters or 1,3-diketones, and unsubstituted or substituted styrenesulfonyl chlorides with electron-withdrawing groups were tolerated.

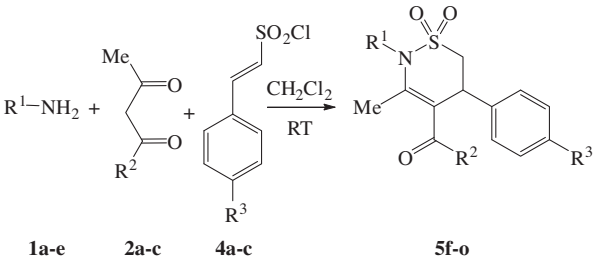
In conclusion, a variety of sultams **5a–o** were synthesized in moderate to good yields via one-pot, three-component reactions of 1,3-dicarbonyl compounds, amines and substituted

Table 1
Reactions of amines **1a–e**, β-ketoester **2a** and styrenesulfonyl chloride (**4a**) to afford δ-sultams **5a–e**



1a-e 2a 4a 5a-e

Entry	R^1	Time (h)	Product	Yield (%)
1	Propyl	12	**5a**	76
2	Butyl	12	**5b**	72
3	*sec*-Butyl	24	**5c**	42
4	Cyclohexyl	24	**5d**	35
5	Benzyl	16	**5e**	73



1a-e 2a-c 4a-c 5f-o

Scheme 2. Synthesis of sultams **5f–o** via the condensation of various amines, 1,3-dicarbonyl compounds and styrenesulfonyl chlorides.

Table 2
Reactions of various amines **1a–e**, 1,3-dicarbonyl compounds **2a–c** and styrenesulfonyl chlorides **4a–c** to afford sultams **5f–o**

Entry	R^1	R^2	R^3	Time (h)	Product	Yield (%)
1	Propyl	OEt	Cl	12	**5f**	83
2	Butyl	OEt	Cl	12	**5g**	67
3	*sec*-Butyl	OEt	Cl	24	**5h**	36
4	Cyclohexyl	OEt	Cl	24	**5i**	37
5	Benzyl	OEt	Cl	12	**5j**	78
6	H	OMe	H	24	**5k**	86
7	H	OMe	Cl	24	**5l**	42
8	Propyl	Me	Br	12	**5m**	77
9	Butyl	Me	H	12	**5n**	66
10	Butyl	Me	Cl	12	**5o**	62

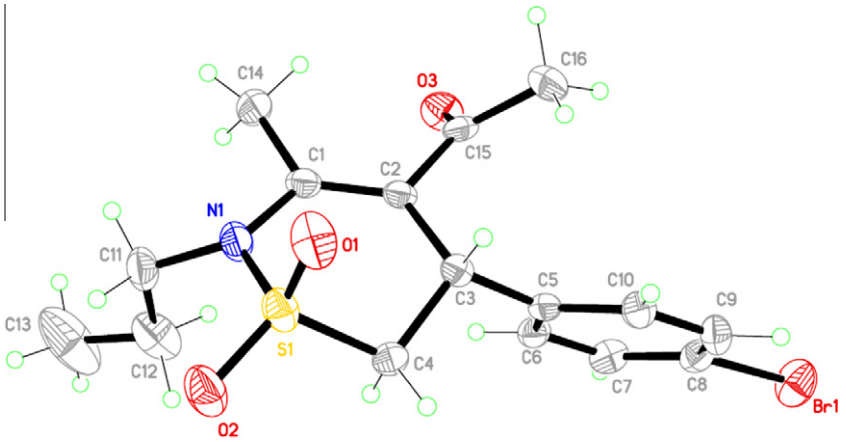


Figure 2. ORTEP diagram of compound **5m**.

styrenesulfonyl chlorides. The six-membered sultams were presumably obtained via N-sulfonylation—intramolecular Michael addition sequences.

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17. *General procedure for the synthesis of sultam* **5a**. To a stirred solution of β-ketoester **2a** (1 mmol, 0.126 mL) was added amine **1a** (1 mmol, 0.082 mL) dropwise. Styrenesulfonyl chloride (**4a**) (1 mmol, 0.202 g) dissolved in CH_2Cl_2 (7 mL) was subsequently added and the mixture stirred for 12 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica gel (230–400 mesh; Merck), using hexane–EtOAc (9:1) as eluent to give sultam **5a**.
18. *Ethyl 3-methyl-5-phenyl-2-propyl-5,6-dihydro-2H-1,2-thiazine-4-carboxylate 1,1-dioxide* (**5a**).White solid, (258 mg, 76%), mp: 79–81 °C; IR (KBr) ν: 1708 (CO), 1323 (SO_2), 1125 (SO_2) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7.0 Hz, 3H, $CH_3CH_2CH_2N$), 0.99 (t, *J* = 7.5 Hz, 3H, CH_3CH_2O), 1.73–1.75 (m, 2H, $CH_3CH_2CH_2N$), 2.29 (d, *J* = 1.5 Hz, 3H, $CH_3C{=}C$), 2.96 (dd, *J* = 13.2, 12.5 Hz, 1H, $SO_2CHHCHPh$), 3.48–3.51 (m, 1H, $SO_2CHHCHPh$), 3.52–3.54 (m, 1H, CH_3CH_2CHHN), 3.72–3.77 (m, 1H, CH_3CH_2CHHN), 3.80 (q, *J* = 7.5, 2H, CH_3CH_2O), 4.44–4.48 (m, 1H, SO_2CH_2CHPh), 7.21–7.33 (m, 5H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5 ($CH_3CH_2CH_2N$), 13.9 (CH_3CH_2O), 19.3 ($CH_3C{=}C$), 23.4 ($CH_3CH_2CH_2N$), 44.2 (SO_2CH_2CHPh), 48.3 ($CH_3CH_2CH_2N$), 53.8 (CH_3CH_2O), 60.8 (SO_2CH_2CHPh), 116.2 (NC═C), 144.53 (NC═C), 127.9, 127.9, 129.3, 141.0 (Ph), 167.4 (OC═O); MS (EI, 70 eV) *m*/*z* 337 (49, M^+), 292 (21), 272 (17), 244 (76), 43 (100%); Anal. calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found: C, 60.29; H, 6.49; N, 4.25.
19. (a) *Ethyl 2-benzyl-3-methyl-5-phenyl-5,6-dihydro-2H-1,2-thiazine-4-carboxylate 1,1-dioxide* (**5e**). White solid (281 mg, 73%); mp: 108–110 °C; IR (KBr) ν: 1715 (CO), 1346 (SO_2); 1158 (SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.0 Hz, 3H, CH_3CH_2O), 2.39 (d, *J* = 2.0 Hz, 3H, $CH_3C{=}C$), 2.59 (dd, *J* = 13.3, 12.5 Hz, 1H, $SO_2CHHCHPh$), 3.37–3.41 (m, 1H, $SO_2CHHCHPh$), 3.85 (q, *J* = 7.0 Hz, 2H, CH_3CH_2O), 4.38–4.42 (m, 1H, SO_2CH_2CHPh), 4.79 (d, *J* = 16.0 Hz, 1H, $PhCHHN$), 5.01 (d, *J* = 16.0 Hz, 1H, $PhCHHN$), 6.91–7.47 (m, 10H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 13.9 (CH_3CH_2O), 20.0 ($CH_3C{=}C$), 44.1 (SO_2CH_2CHPh), 50.3 ($PhCH_2N$), 53.5 (CH_3CH_2O), 60.9 (SO_2CH_2CHPh), 118.6 (NC═C), 144.1 (NC═C), 127.8, 127.9, 128.8, 128.9, 129.2, 129.4, 135.7, 140.5, 167.1 (OC═O); MS (EI, 70 eV) *m*/*z* 385 (4, M^+), 351 (27), 258 (55), 214 (43), 91 (100%). Anal. calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.12; H, 6.23; N, 3.86; (b) *1-[5-(4-bromophenyl)-3-methyl-2-propyl-5,6-dihydro-2H-1,2-thiazin-4-yl]ethanone 1,1-dioxide* (**5m**). Cream solid, (296 mg, 77%); mp: 105–108 °C; IR (KBr) ν 1725 (CO), 1346 (SO_2); 1146 (SO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H, $CH_3CH_2CH_2N$), 1.71–1.78 (m, *J* = 7.6 Hz, 2H, $CH_3CH_2CH_2N$), 1.98 (s, 3H, $CH_3C{=}C$), 2.13 (s, 3H, CH_3CO), 2.92 (t, *J* = 12.7 Hz, 1H, $SO_2CHHCHPh$), 3.46–3.50 (m, 1H, $SO_2CHHCHPh$), 3.51–3.54 (m, 1H, CH_3CH_2CHHN), 3.69–3.73 (m, 1H, CH_3CH_2CHHN), 4.43–4.47 (m, 1H, SO_2CH_2CHPh), 7.10 (d, *J* = 8.2 Hz, 2H, Ph), 7.40 (d, *J* = 8.2 Hz, 2H, Ph); ^{13}C NMR (125 MHz,$CDCl_3$) δ 11.5 ($CH_3CH_2CH_2N$), 19.6 ($CH_3C{=}C$), 23.4 ($CH_3CH_2CH_2N$), 30.8 (CH_3CO), 43.7 (SO_2CH_2CHPh), 48.4 ($CH_3CH_2CH_2N$), 53.8 (SO_2CH_2CHPh), 122.4 (NC═C), 141.2 (NC═C), 129.9, 133.0, 133.2, 138.7, 201.8 (C═O); MS (EI, 70 eV) *m*/*z* 387 [20, M^+ (^{81}Br)], 385 [52, M^+ (^{79}Br)], 329 (61), 250 (55), 236 (94), 41 (100%). Anal. calcd for $C_{16}H_{20}BrNO_3S$: C, 49.75; H, 5.22; N, 3.63. Found: C, 50.12; H, 5.18; N, 3.43.
20. Crystallographic data for **5m** have been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 844991. Copies of these data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail:deposit@ccdc.cam.ac.uk).